PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
W 4494-004 GG		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE01/01627	16/07/2001	17/07/2000
International Patent Classification (IPC) or national classification and IPC A61L27/02		
Applicant BONE SUPPORT AB et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
31/01/2002	14.10.2002
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Peris Antoli, B Telephone No. +49 89 2399 8476

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/SE01/01627

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-21	as originally filed			
Claims, No.:				
1-33	as received on	25/09/2002	with letter of	25/09/2002
Drawings, sheets:				
1/3-3/3	as originally filed			

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
see separate sheet

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-33
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-33
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-33
	No:	Claims	

2. Citations and explanations
see separate sheet

Re Item I

Basis of the report

1. The replacement of the feature "calcium phosphate **cement**" of originally filed claims 1, 13, 14 and 15 by the feature "calcium phosphate **bone substitute**" in present claims 1, 13, 14 and 15 respectively, appears to infringe Article 34(2)(b) PCT (see below).

1.1 Although it is clear from the application as originally filed (see e.g. p. 11, l. 15-16 and p. 15, l. 13) that the hardenable calcium phosphate (Ca/P) used in the second setting reaction component of the claimed composition can be hardened to a Ca/p product suitable as bone substitute, the application as filed contain no precise definition of "*Ca/P bone substitute*" contrarily to the given definition of *"Ca/P cement*" (see p. 7, l. 10-20). Thus, the replacement of the latter feature (i.e. cement) by the former (i.e. bone substitute) may introduce subject-matter which extends beyond the content of the application as originally filed.

1.2 Due to the objection raised above and according to Rule 70.2(c) PCT, claims 1, 13, 14 and 15 have been read as is the aforementioned amendment had not been made. Hence the feature "calcium phosphate **bone substitute**" in said claims has been read as "calcium phosphate **cement**". The remaining claims have been read accordingly.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2. Reference is made to the following documents:
   - D1: WO-A1-8705521
   - D2: WO-A1-9917710
   - D3: Mirchi A. A. et al.: Biomaterials, 1989, no. 9, pp. 634638.
   - D4: Bohmer M. et al.: Bioceramics: materials and applications; 48, 1995, pp. 245-259,
   - D5: WO-A1-9100252
   - D6: WO-A1-9117722

3. Claims 1-33 meet the requirements of Art. 33(2) and 33(3) PCT because their subject matter is new and inventive over the prior art documents cited in the search report (see below).

3.1 **Novelty:**

Independent claim 1 relates to an injectable composition suitable as bone substitute, said composition comprising two different hardenable components (first and second setting reaction components) which are capable of undergoing setting reaction (i.e. hardening) in the presence of aqueous liquids.

None of the prior art documents cited in the search report discloses an injectable bone substitute composition comprising two different hardenable components (see below). Thus, the subject matter of claim 1, as well as that of the dependent claims 2-32 and the related claim 33, is considered to be new.

D1 (see e.g. claims 1 and 6 in conjunction with p. 5, l. 23-29); D2 (see e.g. claims 1 and 9); D3 (see e.g. abstract) and D4 (see e.g. abstract) disclose injectable bone substitute compositions comprising Ca/P and calcium sulphate (CA/S) components. However, in the compositions of D1 the Ca/P component functions as hard filler (i.e. it is already hardened when incorporated to the composition). In the compositions of D2-D4 the Ca/S component (namely Ca-sulphate hemihydrate) functions as so-called setting rate controller, which depending on the concentration used, decreases or increases the setting time of the hardenable Ca/P component (see D4: abstract). Hence, D2-D4 disclose compositions comprising only one hardenable component.

3.2 **Inventive step:**

The problem posed in the present application was to provide injectable bone substitute material capable of being hardened in a body fluid *in vivo*, and which also provides a long-lasting implant with high mechanical strength, which after a period of time presents a porous and irregular structure to allow bone ingrowth.

Said problem is solved with compositions according to claim 1, which are compositions comprising two different hardenable components, namely a determined Ca/P component and a determined Ca/S component, which can be

hardened in a body fluid *in vivo* to a bi-phasic bone substitute implant. Each of the two different hardenable components hardens to a product which, itself, is suitable as bone substitute, but each product has different resorption characteristics. So the hardened Ca/S dihydrate resorbs or degrades rather quickly leaving a porous structure within the long-lasting hardened Ca/P (see e.g. p. 6, l. 19 to p. 7, l. 9 and p. 11, l. 6-16 of the application).

None of the prior art documents cited in the search report, either alone or in combination, suggests an implantable bone substitute composition on the basis of two different hardenable components.
[Note that in the same way as D1-D4, D5 (see e.g. claims 6-8) and D6 (see e.g. claims 1 and 4) only relate to compositions comprising only one hardenable component].

Thus, the claimed subject matter (i.e. that of claims 1-33) involves an inventive step.

4. Claims 1-33 satisfy the criterion set forth in Art. 33(4) PCT because their subject matter is susceptible of industrial application.

CLAIMS

1. An injectable composition for a bone mineral substitute material with the capability of being hardened in a body fluid *in vivo* to a bi-phasic bone substitute implant that with time obtains a porous structure for bone ingrowth, which composition comprises a dry powder mixed with an aqueous liquid, said dry powder comprising
a first setting reaction component, which is a calcium sulphate hemihydrate with the capability of being hardened to a calcium sulphate dihydrate bone substitute when reacting with said aqueous liquid;
a second setting reaction component, which is a calcium phosphate with the capability of being hardened to a calcium phosphate bone substitute when reacting with said aqueous liquid; and
at least one accelerator for the setting reaction of said first and/or second setting reaction component with said aqueous liquid.

2. A composition as in any of claims 1-3, c h a r a c t e r i z e d in that said first and/or said second setting reaction component is in particulate form with a particle size of 1-100 µm, preferably 1-10 µm.

3. A composition as in claim 1, c h a r a c t e r i z e d in that said calcium sulphate hemihydrate is α-calcium sulphate hemihydrate.

4. A composition as in any of claims 1-3, c h a r a c t e r i z e d in that said first setting reaction component comprises 2-80 wt%, preferably 10-30 wt% of said dry powder.

5. A composition as in claim 1, c h a r a c t e r i z e d in that said second setting reaction component is selected from the group comprising tricalcium phosphate (TCP), tetracalcium phosphate (TTCP), anhydrous dicalcium phosphate, monocalcium phosphate monohydrate (MCPM),

dicalcium phosphate dihydrate (DCPD), and octocalcium phosphate (OCP).

6. A composition as in claim 5, characterized in that said tricalcium phosphate is α-tricalcium phosphate.

7. A composition as in any of claims 1-2 or 5-6, characterized in that said second setting reaction component comprises 10-98 wt%, preferably 70-90 wt% of said dry powder.

8. A composition as in claim 1, characterized in that said at least one accelerator for the reaction of said first setting reaction component with said aqueous liquid is particulate calcium sulphate dihydrate.

9. A composition as in claims 8, characterized in that said particulate calcium sulphate dihydrate is α-calcium sulphate dihydrate.

10. A composition as in claim 8 or 9, characterized in that said particulate calcium sulphate dihydrate has a particle size of less than 1 mm.

11. A composition as in claim 10, characterized in that said particulate calcium sulphate dihydrate has a particle size of less than 150 μm, preferably less than 50 μm.

12. A composition as in any of claims 8-11, characterized in that said particulate calcium sulphate dihydrate comprises between 0.1 and 10 wt%, preferably between 0.1 and 2 wt% of said first setting reaction component.

13. A composition as in claim 1, characterized in that said at least one accelerator for the reaction of said second setting reaction component with said aqueous liquid is particulate calcium phosphate bone substitute.

14. A composition as in claim 13, characterized in that said particulate calcium phosphate bone substitute has a Ca/P ratio between 1.5 and 2.

15. A composition as in claim 13 or 14, characterized in that said particulate calcium phosphate bone substitute is hydroxylapatite (HA), tricalcium phosphate (TCP), or a mixture thereof.

16. A composition as in claim 15, characterized in that said hydroxylapatite is precipitated hydroxylapatite (PHA).

17. A composition as in any of claims 13-16, characterized in that said particulate calcium phosphate bone substitute has a particle size which is less than 20 µm, preferably less than 10 µm.

18. A composition as in any of claims 13-17, characterized in that said particulate calcium phosphate bone substitute comprises between 0.1 and 10 wt%, preferably between 0.5 and 5 wt% of said second setting reaction component.

19. A composition as in claim 1, characterized in that said aqueous liquid comprises destilled water or a balanced salt solution.

20. A composition as in claim 1 or 19, , characterized in that said at least one accelerator for the reaction of said second component with said aqueous liquid is dissolved in said aqueous liquid.

21. A composition as in claim 20, characterized in that said accelerator is disodium hydrogen phosphate (Na_2HPO_4).

22. A composition as in claim 20 or 21, , characterized in that said accelerator comprises 0.1-10 wt%, preferably 1-5 wt% of said aqueous liquid.

23. A composition as in claim 1 or 19, characterized in that said aqueous liquid comprises

between 0.1 and 2 ml, preferably between 0.5 and 1 ml per gram of said powder.

24. A composition as in any of claims 1-23, characterized in that up to 95 %, preferably between 80 and 90 %, of said calcium sulphate hemihydrate is replaced by hardened calcium sulphate dihydrate in order to improve the injectability thereof.

25. A composition as in any of claims 1-23, characterized in that it further comprises a biologically compatible oil in order to improve the injectability thereof.

26. A composition as in claim 1, characterized in that said biologically compatible oil is vitamin E.

27. A composition as in claim 26 or 27, , characterized in that said biologically compatible oil comprises between 0.1 and 5 wt%, preferably between 0.5 and 2 wt%.

28. A composition as in any of claims 1-23, characterized in that it further comprises a pH reducing component in order to improve the injectability thereof.

29. A composition as in claim 28, characterized in that said a pH reducing component is ascorbic acid or citric acid.

30. A composition as in claim 28 or 97, , characterized in that said pH reducing component comprises between 0.1 and 5 wt%, preferably between 0.5 and 2 wt%.

31. A composition as in claim 1, characterized in that said dry powder is sterile.

32. A composition as in claim 1, characterized in that it further comprises biologically active substances, such as growth factors and/or anti-cancer substances and/or antibiotics and/or antioxidants.

33. Method of producing an injectable bone mineral substitute material, wherein a composition as in any of claims 1-32 is mixed in a closed mixing and delivery system, preferably under conditions of subatmospheric pressure.